Tetracyclines, Oral
Therapeutic Class Review (TCR)

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FDA-APPROVED INDICATIONS[1]

Tetracycline antibiotics, with the exception of doxycycline hyclate 20 mg, doxycycline monohydrate delayed-release 40 mg (Oracea), and minocycline extended-release (Solodyn ER), are indicated for the treatment of the following infections:

- Ophthalmic infections
  - Trachoma caused by *Chlamydia trachomatis*, although the infectious agent is not always eliminated as judged by immunofluorescence.
  - Inclusion conjunctivitis caused by *Chlamydia trachomatis*.
- Rickettsial infections
  - Rocky Mountain spotted fever, typhus fever and the typhus group, Q fever, rickettsialpox, and tick fevers
- Respiratory tract infections
  - Respiratory tract infections caused by *Mycoplasma pneumoniae*
  - Psittacosis (ornithosis) caused by *Chlamydia psittaci*
  - When bacteriologic testing indicates appropriate susceptibility to the drug
    - Respiratory tract infections caused by *Haemophilus influenzae;*
    - Respiratory tract caused by *Klebsiella* species; and
    - Upper respiratory infections caused by *Streptococcus pneumoniae*.
- Sexually transmitted infections
  - Uncomplicated urethral, endocervical, or rectal infections in adults caused by *Chlamydia trachomatis*
  - Nongonococcal urethritis caused by *Ureaplasma urealyticum*
  - Lymphogranuloma venereum caused by *Chlamydia trachomatis*
  - Granuloma inguinale caused by *Calymmatobacterium granulomatis*
- Specific bacterial infections
  - Plague due to *Yersinia pestis*
  - Tularemia due to *Francisella tularensis*
  - Cholera caused by *Vibrio cholerae*
  - Campylobacter fetus infections caused by *Campylobacter* fetus
  - Brucellosis due to *Brucella* species (in conjunction with streptomycin)
  - Bartonellosis due to *Bartonella bacilliformis*
  - Relapsing fever due to *Borrelia recurrentis*

- Because many strains of the following groups of microorganisms have been shown to be resistant to tetracycline antibiotics, these agents are indicated for treatment of infections caused by the following gram-negative microorganisms, when bacteriologic testing indicates appropriate susceptibility to the drug:
  - ❒ *Escherichia coli*
  - ❒ *Enterobacter aerogenes*
  - ❒ *Shigella* species
  - ❒ *Acinetobacter* species
  - ❒ Urinary tract infections caused by *Klebsiella* species
- Anthrax due to *Bacillus anthracis*, including inhalational anthrax (post-exposure), to reduce the incidence or progression of disease following exposure to aerosolized *Bacillus anthracis*
- Alternative treatment when penicillin is contraindicated
  - ❒ Uncomplicated gonorrhea caused by *Neisseria gonorrhoeae* (with the exception of Doryx)
  - ❒ Syphilis caused by *Treponema pallidum*
  - ❒ Yaws caused by *Treponema pertenue*
  - ❒ Listeriosis due to *Listeria monocytogenes* (with the exception of Doryx)
  - ❒ Vincent's infection caused by *Fusobacterium fusiforme*
  - ❒ Actinomycosis caused by *Actinomyces israelii*
  - ❒ Infections caused by *Clostridium* species
- Acute intestinal amebiasis, as adjunct therapy to amebicides
- Severe acne, as adjunctive therapy

FDA-approved Indications (continued)

Drug	Manufacturer	Additional indication(s)
demeclocycline[2]	generic	▪ Skin and skin structure infections caused by *S. aureus* (Note: not the drug of choice). See package insert for full indications.
doxycycline (Vibramycin®)[3,4,5]	generic, Pfizer	▪ Vibramycin only: Prophylaxis of malaria due to *Plasmodium falciparum* in short-term travelers (< 4 months) to areas with chloroquine and/or pyrimethamine-sulfadoxine resistant strains.
doxycycline monohydrate capsules (Adoxa)[6]	generic, PharmaDerm	▪ Skin and skin structure infections caused by *S. aureus* (Note: not the drug of choice)
doxycycline hyclate tablets (Acticlate)[7]	Aqua	▪ Rickettsial infections ▪ Sexually transmitted infections ▪ Respiratory tract infections ▪ Specific bacterial infections ▪ Anthrax, including inhalational form ▪ Alternate treatment for selected infections when penicillin is contraindicated ▪ Adjunctive therapy in acute intestinal amebiasis and severe acne ▪ Prophylaxis of malaria
doxycycline hyclate 20mg tablets[8]	generic	▪ Adjunct to scaling and root planing to promote attachment level gain and to reduce pocket depth in patients with adult periodontitis
doxycycline hyclate delayed release tablets (Doryx®, Morgidox™)[9,10]	Mayne, Medimetriks	▪ Prophylaxis of malaria due to *Plasmodium falciparum* in short-term travelers (< 4 months) to areas with chloroquine and/or pyrimethamine-sulfadoxine resistant strains.
doxycycline monohydrate delayed release (DR) (Oracea®)[11]	Galderma	▪ Treatment of only inflammatory lesions (papules and pustules) of rosacea in adult patients. Efficacy beyond 16 weeks and safety beyond 9 months have not been established.
minocycline (Dynacin)[12]	generic, Par	▪ Treatment of meningococcal infection ▪ Treatment of symptomatic carriers of *Neisseria meningitidis* to eliminate the meningococci from the nasopharynx ▪ Skin and skin structure infections caused by *S. aureus* (Note: not the drug of choice) ▪ Although no controlled clinical efficacy studies have been conducted, limited clinical data show that oral minocycline has been used successfully in the treatment of infections caused by *Mycobacterium marinum.*
minocycline extended release (ER) (Solodyn®)[13]	generic, Medicis Derm	▪ Treatment of only inflammatory lesions of non-nodular moderate to severe acne vulgaris in patients > 12 years of age.
tetracycline[14]	generic	▪ Respiratory tract infections due to *Streptococcus pyogenes* ▪ Lower respiratory tract infections due to *Streptococcus pyogenes or S. pneumoniae* ▪ Skin and skin structure infections caused by *S. pyogenes* or *S. aureus* (Note: not the drug of choice for infections caused by *S. aureus*) ▪ Infections caused by *N. gonorrhoeae*

OVERVIEW

Tetracyclines have been around since the introduction of chlortetracycline in 1948. Tetracycline antibiotics have similar antimicrobial spectra and safety profiles, and are used for the treatment of a variety of infectious diseases. However, with increasing bacterial resistance to the tetracyclines and with the development of newer antimicrobial agents, the number of uses for these drugs is declining. In patients unable to take penicillin, tetracyclines are an alternative in the treatment of Lyme disease, syphilis, and brucellosis.

The 2015 Centers for Disease Control and Prevention (CDC) sexually transmitted diseases (STD) guidelines no longer recommend doxycycline for the treatment of urethritis.[15] Doxycycline is the alternative agent for the treatment of granuloma inguinale (azithromycin is now the preferred agent); it is still preferred drug to treat lymphogranuloma venereum, cervicitis, and infections due to Chlamydia. In the treatment of mild to moderate pelvic inflammatory disease, outpatient therapy with intramuscular ceftriaxone plus oral doxycycline, with or without oral metronidazole, is recommended. Intramuscular cefoxitin plus oral probenecid plus doxycycline, with or without metronidazole, may also be considered. Doxycycline is a part of the treatment regimen for acute epididymitis and proctitis and STD rectal infections when gonococcal and/or *Chlamydia* infections are presumed. Doxycycline and tetracycline are alternatives for the recommended treatment in syphilis when a patient has a severe penicillin allergy. Doxycycline is preferred over tetracycline due to the potential for greater gastrointestinal intolerance associated with tetracycline.

The joint guidelines from the American Thoracic Society (ATS) and Infectious Diseases Society of America (IDSA) published in 2007 recommend macrolides (e.g., erythromycin, clarithromycin, azithromycin – strong recommendation) or doxycycline (weak recommendation) for adult patients who are otherwise healthy without risk factors for multi-drug resistant *S. pneumoniae*.[16] For adult outpatients with comorbidities including chronic heart, lung, renal, and hepatic disorders; diabetes; alcoholism; malignancies; asplenia; immunosuppression; or use of any antibiotic within the last three months or other risk factors for multi-drug resistant *S. pneumoniae*; first-line therapy may include a respiratory fluoroquinolone (moxifloxacin, gemifloxacin, or levofloxacin) or a beta-lactam plus a macrolide as a strong recommendation. Beta-lactam selection may include high-dose amoxicillin or amoxicillin/clavulanate. Other beta-lactam alternatives include ceftriaxone, cefpodoxime, or cefuroxime. Doxycycline may be used as an alternative to macrolides in combination with a beta-lactam. An update to the IDSA guidelines is in progress and is projected for publication in fall 2016.

The CDC recommends ciprofloxacin, levofloxacin, or doxycycline for the initial treatment of inhalational anthrax. Since there are no safety data available for levofloxacin use beyond 30 days, oral ciprofloxacin and doxycycline are recommended over levofloxacin.[17] Other agents suggested for use in the event the first-line agents are unavailable or not tolerated include moxifloxacin, amoxicillin, and penicillin VK, if the isolate is penicillin susceptible, and clindamycin. Cephalosporins and trimethoprim/sulfamethoxazole should not be used for therapy. Prophylaxis for inhalational anthrax exposure should include 60 days of antimicrobial therapy started as soon after the exposure as possible along with a three-dose series of Anthrax Vaccine Adsorbed. Because of potential adverse effects of prolonged use of ciprofloxacin or doxycycline in children, amoxicillin was an option for completion of the remaining 60 days of therapy for persons infected in the bioterrorist attacks of 2001. Clinical data are very limited for the treatment of anthrax in infants and children. For cutaneous

anthrax, ciprofloxacin and doxycycline also are first-line therapy for adults and children. These CDC guidelines were updated in early 2014.

In the treatment of acne vulgaris, the 2007 guidelines from the American Academy of Dermatology state that systemic antibiotics including tetracyclines (recommendation grade A – consistent and good quality patient-oriented evidence; grade 1 - good quality patient-oriented evidence) are a standard of care in the management of moderate and severe acne and treatment-resistant forms of inflammatory acne.[18] According to the guidelines, doxycycline and minocycline are more effective than tetracycline. For eradication of *Propionibacterium acnes*, there is some evidence that minocycline is superior to doxycycline. Other systemic antibiotics mentioned for the management of moderate to severe acne include erythromycin, trimethoprim, and trimethoprim/sulfamethoxazole. The American Academy of Dermatology is in the process of updating their acne treatment guidelines. Anticipated release is listed as summer 2015, but as of September 15, 2015, there are no new posted guidelines.

The newest tetracycline, tigecycline, is a derivative of minocycline. It is the first agent in a class known as glycylcyclines. This agent is indicated for complicated skin and skin structure infections, as well as intra-abdominal infections. It is only available in an intravenous formulation, so will not be discussed further in this review.

PHARMACOLOGY[19]

The tetracyclines are bacteriostatic. They exert their antimicrobial effect by reversibly binding to the 30S subunit of the bacterial ribosome, preventing the binding of tRNA to the mRNA-ribosome complex, thereby inhibiting protein synthesis and, thus, cell growth. Tetracyclines are active against a wide range of gram-positive and gram-negative organisms and have similar antimicrobial spectra; cross-resistance is common.

Doxycycline and minocycline, both long-acting, are more lipid-soluble and have minimal renal clearance, making these two agents drugs of choice in patients with compromised renal function.

Doxycycline is available in two oral solid dosage formulations – monohydrate and hyclate.[20] Both forms are equally effective, but one form may not be substituted for the other. The bioavailability of doxycycline monohydrate may be lower at high pH which could be clinically significant for patients on long-term acid suppression therapy or patients with gastrectomy or gastric bypass surgery. Monohydrate dosage forms may dissolve slower in the stomach which potentially could reduce gastrointestinal adverse effects. Doxycycline hyclate dosage forms may be taken with food, if stomach irritation occurs.

The action of tetracyclines in the treatment of acne vulgaris is believed to be due in part to their antibacterial actions. Skin bacteria produce lipase that breaks down triglycerides present in sebum into free fatty acids, which are comedogenic and may be the cause of the inflammatory lesions of acne. Antibacterial and anti-inflammatory actions are two possible mechanisms of tetracyclines.

Demeclocycline antagonizes the actions of vasopressin at the collecting duct in the nephron; it produces diuresis by inhibiting ADH-induced water reabsorption in the distal portion of the convoluted tubules. Effects are seen within five days and can be reversed within two to six days following the end of therapy. It has a lower risk of toxicity than lithium for this condition, and is, thereby, favored by clinicians. The clinical use of demeclocycline is limited to treatment of Syndrome of Inappropriate Antidiuretic Hormone (SIADH).[21]

In the treatment of periodontitis, it is thought that doxycycline works by inhibiting collagenase which breaks down connective tissue and leads to the separation of the gum from the tooth. The exact mechanism, however, is not known.

Spectrum of Activity

The tetracyclines are active against gram-positive and gram-negative bacteria. Doxycycline is typically active against *Bacillus anthracis, Listeria monocytogenes*, and *S. aureus,* although tetracyclines are not the drug of choice in the treatment of any type of staphylococcal infection. The tetracyclines are unreliable against streptococcal infections, as resistance rates have been reported to be 50%. Use of any tetracycline for a streptococcal infection should be guided by culture and sensitivity data. Doxycycline is typically effective against the following gram-negative organisms: *Bartonella bacilliformis, Brucella species, Calymmatobacterium granulomatis, Campylobacter fetus, Francisella tularensis, Haemophilus ducreyi, Haemophilus influenzae, Neisseria gonorrhoeae, Vibrio cholerae,* and *Yersinia pestis*. Culture and sensitivity data for other gram-negative organisms should be consulted. Most of the *Rickettsia* bacteria are susceptible to the tetracyclines. Tetracycline is commonly used in combination with bismuth salts and metronidazole plus acid suppression therapy in the treatment of *H. pylori*.

PHARMACOKINETICS[22]

Drug	Half-life (hrs)	Elimination (%)
demeclocycline	10-17	Urine: 42 Feces: 42
doxycycline[23,24,25]	18-22	Doxycycline is excreted in the urine and feces as unchanged drug.
doxycycline monohydrate (Adoxa TT, Adoxa CK)[26]	16.33	
doxycycline monohydrate (Monodox)[27]	n/a	
doxycycline hyclate (Acticlate)[28]	18-22	
doxycycline hyclate DR (Doryx)[29]	18-22	
doxycycline monohydrate delayed release (DR) (Oracea)*[30]	23.2	
doxycycline hyclate[31]	18	
minocycline	11-22	Partially metabolized Renal: 4-19 Feces: reported
minocycline extended release (ER) (Solodyn)[32]	n/a	
tetracycline	6-12	Urine: 60 Feces: reported

*Capsules contain two types of beads for biphasic release: immediate release and delayed release in a 3:1 ratio, respectively.

n/a = not available

CONTRAINDICATIONS/WARNINGS[33,34,35,36,37,38,39,40,41]

These agents are contraindicated in any persons with hypersensitivity to the active ingredient or to any of the tetracyclines.

The use of drugs of the tetracycline class during tooth development (last half of pregnancy, infancy, and childhood to the age of eight years) may cause permanent discoloration of the teeth (yellow-gray-brown). This adverse effect is more common during long-term use of the drugs but has been observed following repeated short-term courses. Enamel hypoplasia has also been reported. Tetracycline drugs, therefore, should not be used in this age group, except for anthrax, including inhalational anthrax (post-exposure), unless other drugs are not likely to be effective or are contraindicated.

All tetracyclines form a stable calcium complex in any bone-forming tissue. A decrease in the fibula growth rate has been observed in premature infants given oral tetracycline in doses of 25 mg/kg every six hours. This reaction was shown to be reversible when the drug was discontinued.

Clostridium difficile-associated diarrhea (CDAD) has been reported with use of nearly all antibacterial agents, including the tetracycline class, and may range in severity from mild diarrhea to fatal colitis. Treatment with antibacterial agents alters the normal flora of the colon, leading to overgrowth of *C. difficile*. *C. difficile* produces toxins A and B which contribute to the development of CDAD. Hypertoxin-producing strains of *C. difficile* cause increased morbidity and mortality, as these infections can be refractory to antimicrobial therapy and may require colectomy. CDAD must be considered in all patients who present with diarrhea following antibiotic use. A detailed medical history is necessary since CDAD has been reported to occur over two months after the administration of antibacterial agents. If CDAD is suspected or confirmed, ongoing antibiotic use not directed against *C. difficile* may need to be discontinued. Appropriate fluid and electrolyte management, protein supplementation, antibiotic treatment of *C. difficile*, and surgical evaluation should be instituted as clinically indicated. If pseudomembranous colitis occurs while on either minocycline ER (Solodyn) or doxycycline DR (Oracea), discontinue the drug.

As with other antibiotic preparations, use of tetracyclines may result in overgrowth of nonsusceptible organisms, including fungi. If superinfection occurs, the antibiotic should be discontinued and appropriate therapy should be instituted. Doxycycline hyclate 20 mg should be used with caution in patients with a history or predisposition to oral candidiasis.

The anti-anabolic action of the tetracyclines may cause an increase in blood urea nitrogen (BUN). Studies to date indicate that this does not occur with the use of doxycycline in patients with impaired renal function.

Photosensitivity manifested by an exaggerated sunburn reaction has been observed in some individuals taking tetracyclines. Patients apt to be exposed to direct sunlight or ultraviolet light should be advised that this reaction can occur with tetracycline drugs, and treatment should be discontinued at the first evidence of skin erythema.

Tetracycline agents are known to cause hyperpigmentation. Tetracycline therapy may induce hyperpigmentation in many organs, including nails, bone, skin, eyes, thyroid, visceral tissue, oral cavity (teeth, mucosa, alveolar bone), sclera, and heart valves. Skin and oral pigmentation has been reported to occur independently of time or amount of drug administration, whereas other pigmentation has been reported to occur upon prolonged administration. Skin pigmentation includes diffuse pigmentation, as well as over sites of scars or injury.

Pseudotumor cerebri (benign intracranial hypertension) in adults has been associated with the use of tetracyclines. The usual clinical manifestations are headache and blurred vision. Bulging fontanels have been associated with the use of tetracyclines in infants. While both of these conditions and related symptoms usually resolve soon after discontinuation of the tetracycline, the possibility for permanent sequelae exists.

Administration of demeclocycline has resulted in appearance of the diabetes insipidus syndrome (polyuria, polydipsia, and weakness) in some patients on long-term therapy. The syndrome has been shown to be nephrogenic, dose-dependent, and reversible on discontinuance of therapy.

Central nervous system (CNS) adverse effects, including dizziness, vertigo, and lightheadedness, may occur with demeclocycline and minocycline. Patients experiencing CNS adverse effects should be cautioned about driving vehicles and using hazardous machinery while on therapy. The symptoms may disappear during therapy and usually rapidly disappear upon discontinuation of minocycline.

Hepatotoxicity has been reported with minocycline; therefore, if liver injury is suspected, discontinue minocycline (Solodyn). Minocycline should be used with caution in patients with hepatic dysfunction and in conjunction with other hepatotoxic drugs. Tetracyclines have been associated with the development of autoimmune syndromes. The long-term use of minocycline in the treatment of acne has been associated with drug-induced lupus-like syndrome, autoimmune hepatitis, and vasculitis.

Drug Rash with Eosinophilia and Systemic Symptoms (DRESS), including fatal cases, has been reported with minocycline use. If this syndrome is recognized, the drug should be discontinued immediately.

Doxycycline syrup (Vibramycin Syrup) contains sodium metabisulfite, a sulfite that may cause allergic-type reactions, including anaphylactic symptoms and life-threatening or less severe asthmatic episodes in certain susceptible people. The overall prevalence of sulfite sensitivity in the general population is unknown and probably low. Sulfite sensitivity is seen more frequently in asthmatic than in non-asthmatic people.

The plasma concentrations of doxycycline (Oracea) achieved during administration are less than the concentration required to treat bacterial diseases. *In vivo* microbiological studies utilizing a similar drug exposure for up to 18 months demonstrated no detectable long-term effects on bacterial flora of the oral cavity, skin, intestinal tract, and vagina. The Oracea dosage form of doxycycline should not be used for treating bacterial infections, providing antibacterial prophylaxis, or reducing the numbers or eliminating microorganisms associated with any bacterial disease.

DRUG INTERACTIONS[42,43,44,45,46,47,48,49,50]

Tetracyclines, as a class, have been shown to increase levels of anticoagulants. Monitor INR for patients on warfarin therapy. Patients who are on anticoagulant therapy may require downward adjustment of their anticoagulant dosage when on concurrent tetracycline therapy.

Concurrent use of a tetracycline may render oral contraceptives less effective. Female patients are advised to use a second form of contraceptive during treatment with tetracycline.

Since bacteriostatic drugs may interfere with the bactericidal action of penicillin, it is advisable to avoid giving tetracyclines in conjunction with penicillin. Absorption of tetracyclines is impaired by antacids containing aluminum, calcium, or magnesium, and iron-containing preparations. Barbiturates, carbamazepine, and phenytoin decrease the half-life of doxycycline. The concurrent use of tetracycline and methoxyflurane has been reported to result in fatal renal toxicity. There is an increased risk of ergotism when ergot alkaloids or their derivatives are given with tetracyclines.

Reports of pseudotumor cerebri (benign intracranial hypertension) have been associated with the concomitant use of isotretinoin and tetracyclines. Since both oral retinoids, including isotretinoin and acitretin, and the tetracyclines, primarily minocycline, can cause increased intracranial pressure, their concurrent use should be avoided.

Divalent and trivalent cations bind with and inhibit oral absorption of tetracyclines. Doxycycline appears to have a lower affinity for calcium and a higher affinity for iron than the other agents. Because of the binding, it is advisable to take oral tetracyclines on an empty stomach.

ADVERSE EFFECTS[51,52,53,54,55,56,57,58,59,60]

The following adverse effects have been reported in patients receiving tetracyclines:

Gastrointestinal: Anorexia, nausea, vomiting, diarrhea, glossitis, dysphagia, enterocolitis, pancreatitis, inflammatory lesions (with monilial overgrowth) in the anogenital region, increases in liver enzymes, and hepatic toxicity (including hepatitis and liver failure)

Due to virtually complete absorption of oral doxycycline and oral minocycline, adverse effects of the lower bowel, particularly diarrhea, have been infrequent. With minocycline, stomatitis, dysphagia, and enamel hypoplasia have been reported.

Instances of esophageal ulcerations have been reported in patients receiving oral tetracyclines. Most of the patients were reported to have taken the medication immediately before lying down.

With minocycline, additional hepatic adverse effects have included hyperbilirubinemia, hepatic cholestasis, and jaundice. Hepatitis, including autoimmune hepatitis, and liver failure have been reported with minocycline use. Lupus-like symptoms have also been reported with minocycline use.

Skin: Maculopapular and erythematous rashes, erythema multiforme.

Exfoliative dermatitis has been reported but is uncommon. Fixed drug eruptions and Stevens-Johnson Syndrome have been reported rarely. Lesions occurring on the glans penis have caused balanitis. Pigmentation of the skin and mucous membranes has also been reported. Photosensitivity can occur. When compared with tetracycline, demeclocycline is associated with a higher incidence of phototoxicity. With minocycline, alopecia, erythema nodosum, hyperpigmentation of nails, pruritus, toxic epidermal necrolysis, and vasculitis have been reported.

Renal Toxicity: Acute renal failure.

Rises in BUN have been reported and is apparently dose-related. Nephrogenic diabetes insipidus has been reported.

Hypersensitivity Reactions: Urticaria, angioneurotic edema, polyarthralgia, anaphylaxis, anaphylactoid purpura, pericarditis, exacerbation of systemic lupus erythematosus, lupus-like syndrome, pulmonary infiltrates with eosinophilia

Hematologic: Hemolytic anemia, thrombocytopenia, neutropenia, and eosinophilia have been reported.

With minocycline, agranulocytosis and pancytopenia have been reported.

CNS: Pseudotumor cerebri (benign intracranial hypertension) in adults; this condition usually resolves after discontinuation, but there is the possibility of permanent vision loss. If visual disturbances occur during treatment, see an ophthalmologist. Intracranial pressure can remain elevated for weeks after discontinuing drug; monitor patients until the pressure stabilizes, monitor dizziness, headache, tinnitus, visual disturbances, and myasthenic syndrome.

With minocycline, convulsions, headache, sedation, vertigo, hypesthesia, tinnitus, decreased hearing, and paresthesia have also been reported.

Musculoskeletal: With minocycline, arthralgia, arthritis, bone discoloration, myalgia, joint stiffness, and joint swelling have been reported.

Other: When given over prolonged periods, tetracyclines have been reported to produce brown-black microscopic discoloration of thyroid glands. No abnormalities of thyroid function studies are known to occur. Very rare cases of abnormal thyroid function have been reported.

Tooth discoloration has occurred in pediatric patients less than eight years of age and has been reported rarely in adults.

SPECIAL POPULATIONS[61,62,63,64,65,66,67,68,69]

Pediatrics

Use of tetracycline products in children less than eight years of age is not recommended due to the potential for tooth discoloration; an exception to this is the use of doxycycline for inhalation anthrax (post-exposure). Safety and effectiveness of minocycline ER (Solodyn) in children less than 12 years of age have not been established.

Pregnancy

All agents in this class are Pregnancy Category D.

Nursing Mothers

The American Academy of Pediatrics considers tetracyclines, including doxycycline, to be usually compatible with breastfeeding because the amount of drug absorbed by infants is small, but little is known about the safety of long-term use.[70] Mothers concerned about the use of doxycycline for antimicrobial prophylaxis should consider expressing and then discarding breast milk so that breastfeeding can be resumed when antimicrobial prophylaxis is completed. Decisions about antimicrobial choice and continuation of breastfeeding should be made by the mother and the healthcare providers of both the mother and the infant.

Renal Impairment

If renal impairment is present, minocycline (Solodyn) doses may need to be adjusted to avoid excessive systemic accumulation of the drug and possible liver toxicity.

DOSAGES

Drug	Usual Dosing	Availability
demeclocycline[71]	**Adults:** 150 mg 4 times daily or 300 mg twice daily Gonorrhea patients sensitive to penicillin: initial oral dose of 600 mg followed by 300 mg every 12 hours for 4 days to a total of 3 g **Pediatrics > 8 years**: 7-13 mg/kg/day depending on severity of disease, divided into 2 to 4 doses, not to exceed dosage of 600 mg daily	150, 300 mg tablets
doxycycline[72, 73, 74, 75, 76]	**Adults:** 100 mg twice daily for most infections; duration of therapy is typically 7 to 10 days, but duration may depend on severity of infection Inhalational anthrax: 100 mg twice daily for 60 days Prophylaxis of malaria: 100 mg daily beginning 1 to 2 days before travel and continuing for 4 weeks after leaving malarious area Dental: 20 mg twice daily at 12-hour intervals, usually in the morning and evening **Pediatrics > 8 years and < 45 kg**: 2.2 mg/kg give twice daily on Day 1, then 2.2 mg/kg daily. For more severe infections, up to 4.4 mg/kg may be used. If > 45 kg, then use adult dosing Prophylaxis for malaria: 2 mg/kg once daily (not to exceed 100 mg) The contents of Doryx tablets (doxycycline delayed-release pellets) may be sprinkled on a spoonful of applesauce. The delayed-release pellets must not be crushed, chewed, or damaged when breaking up the tablet.	doxycycline hyclate: 20, 50, 100 mg capsules; 20, 50, 100 mg tablets doxycycline hyclate DR: 75, 100, 150 mg delayed release tablet; 75, 100, , mg delayed release capsules (Doryx) doxycycline monohydrate: 50, 75, 100, 150 mg capsules 50, 75, 100, 150 mg tablets 25 mg/5mL oral suspension doxycycline calcium: 50 mg/5mL suspension (Vibramycin)
doxycycline hyclate (Acticlate)[77]	Adults: 200 mg on first day (given as 100 mg every 12 hours) followed by a maintenance dose of 100 mg daily. Pediatrics (>8 years): ≤45 kg 4.4 mg per kg of body weight divided into 2 doses the first day, followed by 2.2 mg per kg given as either a single daily dose, or divided into 2 doses on subsequent days. For those weighing >45 kg, use the adult dosing schedule.	75mg and 150 mg scored tablet
doxycycline hyclate[78]	20 mg every 12 hours as an adjunct following scaling and root planing may be administered for up to 9 months.	20 mg tablet
doxycycline monohydrate DR (Oracea)[79]	**Adults:** 1 capsule daily in the morning on an empty stomach, preferably at least 1 hour prior to or 2 hours after meals; Oracea differs from doxycycline used to treat infections; Exceeding recommended dosage can result in higher incidence of adverse effects	40 mg capsules with 30 mg immediate release and 10 mg delayed release beads

Dosages (continued)

Drug	Usual Dosing	Availability
minocycline ER (Solodyn ER)[80]	**Age 12 years and older:** 1mg/kg once daily for 12 weeks. Swallow whole, do not crush chew or split tablets; may be taken with or without food	55, 65, 80, 105, 115 mg extended release tablets
minocycline[81]	**Adults:** 200 mg initially followed by 100 mg every 12 hours or 2 or 4 50 mg pellet-filled capsules may be given initially followed by one 50 mg capsule 4 times daily **Pediatrics:** 4 mg/kg initially followed by 2 mg/kg every 12 hours, not to exceed the usual adult dose Minocin pellet-filled capsules may be taken with or without food; swallow whole	50, 100 mg pellet-filled capsules 50, 75, 100 mg capsules 50, 75, 100 mg tablets
tetracycline[82]	**Adults:** 250-500 mg every 6 hours or 500-1,000 mg every 12 hours; duration of therapy dependent on type and severity of infection Acne rosacea: 250-1,500 mg per day Inflammatory acne vulgaris: 125-250 mg every 6 hours then taper to 125-500 mg daily or every other day **Pediatrics:** 25 to 50 mg/kg divided in 4 equal doses, not to exceed the usual adult dose	250, 500 mg capsules

Brand Periostat for doxycycline hyclate 20 mg tablets is no longer available.

Administration of adequate amounts of fluid along with capsule and tablet forms of drugs in the tetracycline class is recommended to reduce the risk of esophageal irritation and ulceration.[83] Foods and some dairy products interfere with demeclocycline and tetracycline absorption. Oral forms of these agents should be given at least one hour before or two hours after meals. Doxycycline and minocycline may be given with or without food. If gastric irritation occurs, it is recommended that doxycycline be given with food or milk.

CLINICAL TRIALS

Search Strategy

Articles were identified through searches performed on PubMed and review of information sent by manufacturers. Search strategy included the FDA-approved use of all drugs in this class. Randomized, controlled, comparative trials are considered the most relevant in this category. Studies included for analysis in the review were published in English, performed with human participants, and randomly allocated participants to comparison groups. In addition, studies must contain clearly stated, predetermined outcome measure(s) of known or probable clinical importance, use data analysis techniques consistent with the study question, and include follow-up (endpoint assessment) of at least 80% of participants entering the investigation. Despite some inherent bias found in all studies including those sponsored and/or funded by pharmaceutical manufacturers, the studies in this therapeutic class review were determined to have results or conclusions that do not suggest systematic error in their experimental study design. While the potential influence of manufacturer sponsorship and/or funding must be considered, the studies in this review have also been evaluated for validity and importance.

Much of the comparative literature within the class was published 20 to 30 years ago. Comparative literature for the tetracycline class was performed in the 1970s and 1980s. In the treatment of acne, minocycline was found to provide a more rapid response than tetracycline in two double-blind studies.[84,85] In another study, minocycline had superior antibacterial action and reduced the incidence of bacterial resistance in acne patients compared to tetracycline.[86] In an earlier double-blind study, minocycline 50 mg twice daily and tetracycline 250 mg twice daily had similar efficacy in the treatment of acne vulgaris.[87] When compared to other commonly used acne treatments, one study found minocycline to have the least improvement in lesions when compared to either erythromycin, oxytetracycline, or benzoyl peroxide alone.[88]

Doxycycline and tetracycline were compared in a small study of 24 patients with ocular rosacea.[89] Efficacy, based on subjective measures by the patients, was greater with tetracycline (p=0.041) at six weeks; however, after three months of treatment, symptoms scores were similar in both groups. Gastrointestinal adverse effects occurred more frequently with tetracycline (37.5%) than with doxycycline (12.5%). A more recent small study (n=15) published in 2014 showed markedly lessened symptom complaints in patients with ocular rosacea when they received low-dose once daily oral doxycycline.[90]

More recently, the tetracyclines have been compared in open-label trials to agents in other drug classes, such as azithromycin, tazarotene, oxytetracycline, benzoyl peroxide, and topical erythromycin.[91,92,93]

The newer extended release dosage forms of doxycycline DR (Oracea) and minocycline ER (Solodyn) have only been compared to placebo in published literature.[94,95] Each agent showed significant improvement over placebo. The delayed release form of doxycycline taken once daily proved to be effective in treating papulopustular rosacea in both males and females. Treatment success was achieved after 12 weeks of therapy in 73.2% of males (172 per 235) and 75.2% of females (444 per 591).[96]

META-ANALYSIS

A systematic review of the evidence of minocycline in the treatment of acne vulgaris identified randomized controlled trials (RTCs) of minocycline for acne vulgaris.[97] Articles were identified by searching the following databases: MEDLINE, EMBASE, Cochrane Skin Group's Trial Register, CENTRAL, LILACS, and a search of trial registers and reference lists. A total of 39 randomized controlled trials (6,013 participants) met the inclusion criteria and were included. The comparators used were minocycline at any dose compared to either an active control or a placebo in participants with inflammatory acne vulgaris. Outcome measures used in the trials included lesion counts, acne grades/severity scores, participant and doctor global assessments, adverse effects, and drop-out rates. The identified RCTs were generally small and of poor quality. Although minocycline was shown to be an effective treatment for acne vulgaris, there was no evidence showing it to be superior to any other commonly used acne treatment. Minocycline is likely to be an effective treatment for moderate acne vulgaris, but no reliable trial evidence exists to justify its use as first-line therapy. Its efficacy and safety relative to other acne therapies could not be reliably determined due to the poor methodological quality of the trials and lack of consistent choice of outcome measures.

SUMMARY

Tetracyclines are used in the treatment of a variety of infections in adults and children over age of eight years. Adverse effects common to the tetracyclines include gastrointestinal complaints and risk for esophageal ulceration.

Doxycycline is the antibiotic of choice among the tetracyclines for infections involving the upper respiratory tract, sexually transmitted diseases, and the urogenital tract (prostatitis, cervicitis, and urethritis). Doxycycline possesses unique characteristics, such as a broad spectrum of activity, a long serum half-life, greater tissue penetration, and excellent oral absorption, which contribute to its clinical superiority over tetracycline. The drug is not eliminated by the kidneys as is tetracycline and is, therefore, the drug of choice when a tetracycline is indicated in patients with renal dysfunction and in hemodialysis patients. Doxycycline is also a preferred agent to prevent inhalational anthrax after confirmed or suspected aerosol exposure to *B. anthracis*.

Specific dosage forms and indications of a few of the tetracyclines are now available. Doxycycline DR (Oracea) is only indicated for the treatment of inflammatory lesions (papules and pustules) of rosacea in adults. It does not have a significant effect for generalized erythema of rosacea and has not been evaluated for treatment of erythematous, telangiectatic, or ocular components of rosacea, or in the prevention and treatment of infections. Minocycline ER (Solodyn) is only indicated for the treatment of inflammatory lesions of non-nodular moderate to severe acne vulgaris. Comparative literature for these agents is lacking. Doxycycline hyclate 20 mg tablets are indicated as adjunctive therapy to scaling and root planing in reducing pocket depths and increasing periodontal attachment levels in patients with periodontal disease.

Demeclocycline is used infrequently for the treatment of infections. The clinical use of demeclocycline is limited to treatment of Syndrome of Inappropriate Antidiuretic Hormone (SIADH). In a limited number of trials, demeclocycline has been effective in the treatment of water intoxication and inappropriate antidiuretic hormone secretion. When compared with tetracycline, demeclocycline is associated with a higher incidence of phototoxicity.

REFERENCES

1 Available at: www.clinicalpharmacology.com. Accessed September 21, 2015.
2 Demeclocycline [package insert]. Cincinnati, OH; Patheon Pharmaceuticals; July 2014.
3 Vibramycin [package insert]. New York, NY; Pfizer; September 2014. *note: avail as: monohydrate, hyclate, calcium, and hydrochloride hemiethanolate hemihydrate.
4 Doxycycline [package insert]. Eatontown, NJ: West-Ward Pharmaceuticals; November 2011.
5 Available at: www.clinicalpharmacology.com. Accessed September 21, 2015.
6 Adoxa [package insert]. Melville, NY; Pharmaderm; February 2012.
7 Acticlate [package insert]. West Chester, PA; Aqua Pharms; July 2014.
8 Doxycycline hyclate tabs [package insert]. Philadelphia, PA; Lannett; August 2007.
9 Doryx [package insert]. Greenville, NC; Mayne Pharma; May 2015.
10 Morgidox [package insert]. Fairfield, NJ; Medimetriks; January 2011.
11 Oracea [package insert]. Fort Worth, TX; Galderma Laboratories; August 2013.
12 Dynacin [package insert]. Spring Valley, NY; Par Pharmaceuticals; November 2011.
13 Solodyn [package insert]. Scottsdale, AZ; Medicis; October 2013.
14 Available at: www.clinicalpharmacology.com. Accessed September 21, 2015.
15 Centers for Disease Control and Prevention. Sexually Transmitted Diseases Treatment Guidelines, 2015. MMWR 2010; 59 (No. RR-#12):1-114. Available at: http://www.cdc.gov/mmwr/preview/mmwrhtml/rr6403a1.htm. Accessed September 15, 2015.
16 Mandell LA, Wunderink RG, Anzueto A, et al. Infectious Diseases Society of America/American Thoracic Society Consensus Guidelines on the Management of Community-Acquired Pneumonia in Adults. Clin Infect Dis. 2007; 44(Suppl 2):S27-S72.
17 CDC. Available at: http://wwwnc.cdc.gov/eid/article/20/2/13-0687_article. Accessed September 15, 2015.
18 Strauss JS, Krowchuk DP, Leyden JJ, et al for the American Academy of Dermatology. Guidelines of care for acne vulgaris management. J Am Acad Dermatol. 2007; 56(4):651-63.
19 Available at: www.clinicalpharmacology.com. Accessed September 15, 2015.
20 Available at: http://www.pharmacistsletter.com/(S(nbcadcv1ootgo145n2ronz55))/pl/Rumor.aspx?cs=&s=PL&fpt=56&rtid=265. Accessed September 15, 2015.
21 Available at: www.clinicalpharmacology.com. Accessed September 15, 2015.
22 Available at: www.clinicalpharmacology.com. Accessed September 15, 2015.
23 Available at: www.clinicalpharmacology.com. Accessed September 15, 2015.
24 Periostat [package insert]. Fort Worth, TX; Galderma Laboratories; October 2003.
25 Doryx [package insert]. Greenville, NC; Mayne Pharma; May 2015.
26 Adoxa [package insert]. Melville, NY; PharmaDerm; February 2012.
27 Monodox [package insert]. Morristown, NJ; Watson Pharma; February 2011.
28 Acticlate [package insert]. West Chester, PA; Aqua Pharms; July 2014
29 Doryx [package insert]. Greenville, NC; Mayne Pharma; May 2015.
30 Oracea [package insert]. Fort Worth, TX; Galderma Laboratories; August 2013.
31 Doxycycline hyclate tabs [package insert]. Philadelphia, PA; Lannett; August 2007.
32 Solodyn [package insert]. Scottsdale, AZ; Medicis; October 2013.
33 Available at: www.clinicalpharmacology.com. Accessed September 15, 2015.
34 Adoxa [package insert]. Melville, NY; PharmaDerm; February 2012.
35 Oracea [package insert]. Fort Worth, TX; Galderma Laboratories; August 2013.
36 Monodox [package insert]. Morristown, NJ; Watson Pharma; February 2011.
37 Acticlate [package insert]. West Chester, PA; Aqua Pharms; July 2014
38 Doxycycline hyclate tabs [package insert]. Philadelphia, PA; Lannett; August 2007.
39 Solodyn [package insert]. Scottsdale, AZ; Medicis; October 2013.
40 Vibramycin [package insert]. New York, NY; Pfizer; September 2014.
41 Doryx [package insert]. Greenville, NC; Mayne Pharma; May 2015.
42 Available at: www.clinicalpharmacology.com. Accessed September 15, 2015.
43 Adoxa [package insert]. Melville, NY; PharmaDerm; February 2012.
44 Oracea [package insert]. Fort Worth, TX; Galderma Laboratories; August 2013.
45 Monodox [package insert]. Morristown, NJ; Watson Pharma; February 2011.
46 Acticlate [package insert]. West Chester, PA; Aqua Pharms; July 2014
47 Doxycycline hyclate tabs [package insert]. Philadelphia, PA; Lannett; August 2007.
48 Solodyn [package insert]. Scottsdale, AZ; Medicis; October 2013.
49 Vibramycin [package insert]. New York, NY; Pfizer; September 2014.
50 Doryx [package insert]. Greenville, NC; Mayne Pharma; May 2015.
51 Available at: www.clinicalpharmacology.com. Accessed September 15, 2015.
52 Adoxa [package insert]. Melville, NY; PharmaDerm; February 2012.
53 Oracea [package insert]. Fort Worth, TX; Galderma Laboratories; August 2013.
54 Monodox [package insert]. Morristown, NJ; Watson Pharma; February 2011.
55 Acticlate [package insert]. West Chester, PA; Aqua Pharms; July 2014
56 Doxycycline hyclate tabs [package insert]. Philadelphia, PA; Lannett; August 2007.
57 Solodyn [package insert]. Scottsdale, AZ; Medicis; October 2013.
58 Vibramycin [package insert]. New York, NY; Pfizer; September 2014.

59 Doryx [package insert]. Greenville, NC; Mayne Pharma; May 2015.
60 Available at: http://www.micromedexsolutions.com/home/dispatch. Accessed September 10, 2015.
61 Available at: www.clinicalpharmacology.com. Accessed September 15, 2015.
62 Adoxa [package insert]. Melville, NY; PharmaDerm; February 2012.
63 Oracea [package insert]. Fort Worth, TX; Galderma Laboratories; August 2013.
64 Monodox [package insert]. Morristown, NJ; Watson Pharma; February 2011.
65 Acticlate [package insert]. West Chester, PA; Aqua Pharms; July 2014
66 Doxycycline hyclate tabs [package insert]. Philadelphia, PA; Lannett; August 2007.
67 Solodyn [package insert]. Scottsdale, AZ; Medicis; October 2013.
68 Vibramycin [package insert]. New York, NY; Pfizer; September 2014.
69 Doryx [package insert]. Greenville, NC; Mayne Pharma; May 2015.
70 American Academy of Pediatrics Committee on Drugs. The transfer of drugs and other chemicals into human milk. Pediatrics. 2001;108:776--89
71 Declomycin [package insert]. Coral Gables, FL; Glades Pharmaceuticals; June 2007.
72 Adoxa [package insert]. Melville, NY; PharmaDerm; February 2012.
73 Vibramycin [package insert]. New York, NY; Pfizer; September 2014.
74 Doxycycline hyclate tabs [package insert]. Philadelphia, PA; Lannett; August 2007.
75 Available at: www.clinicalpharmacology.com. Accessed September 15, 2015.
76 Doryx [package insert]. Greenville, NC; Mayne Pharma; May 2015.
77 Acticlate [package insert]. West Chester, PA; Aqua Pharms; July 2014
78 Doxycycline hyclate tabs [package insert]. Philadelphia, PA; Lannett; August 2007.
79 Oracea [package insert]. Fort Worth, TX; Galderma Laboratories; August 2013.
80 Solodyn [package insert]. Scottsdale, AZ; Medicis; October 2013.
81 Minocin [package insert]. Cranford, NJ; Triax Pharmaceuticals; August 2010.
82 Available at: www.clinicalpharmacology.com. Accessed September 15, 2015.
83 Available at: www.clinicalpharmacology.com. Accessed September 15, 2015.
84 Samuelson JS. An accurate photographic method for grading acne: initial use in a double-blind clinical comparison of minocycline and tetracycline. J Am Acad Dermatol. 1985; 12(3):461-7.
85 Hubbell CG, Hobbs ER, Rist T, et al. Efficacy of minocycline compared with tetracycline in treatment of acne vulgaris. Arch Dermatol. 1982; 118(12):989-92.
86 Eady EA, Cove JH, Holland KT, et al. Superior antibacterial action and reduced incidence of bacterial resistance in minocycline compared to tetracycline-treated acne patients. Br J Dermatol. 1990; 122(2):233-44.
87 Cullen SI, Cohan RH. Minocycline therapy in acne vulgaris. Cutis. 1976; 17(6):1208-10, 1214.
88 Ozolins M, Eady EA, Avery A, Cunliffe WJ, O'Neill C, Simpson NB, Williams HC. Randomised controlled multiple treatment comparison to provide a cost-effectiveness rationale for the selection of antimicrobial therapy in acne. Health Technol Assess. 2005 Jan;9(1):iii-212.
89 Frucht-Pery J, Sagi E, Hemo I. et al. Efficacy of doxycycline and tetracycline in ocular rosacea. Am J Ophthalmol. 1993; 116(1):88-92.
90 Sobolewska B, Doycheva D, Deuter C, et al. Treatment of ocular rosacea with once-daily low-dose doxycycline. Cornea. 2014; Mar;33(3):257-60. Doi 10.1097/ICO.0000000000000051.
91 Akhyani M, Ehsani AH, Ghiasis M, et al. Comparison of efficacy of azithromycin vs. doxycycline in the treatment of rosacea: a randomized open clinical trial. Int J Dermatol. 2008; 47(3):284-8.
92 Leyden J, Thiboutot DM, Shalita AR, et al. Comparison of tazarotene and minocycline maintenance therapies in acne vulgaris: a multicenter, double-blind, randomized, parallel-group study. Arch Dermatol. 2006; 142(5):605-12.
93 Ozolins M, Eady EA, Avery AJ, et al. Comparison of five antimicrobial regimens for treatment of mild to moderate inflammatory facial acne vulgaris in the community: randomized controlled trial. Lancet. 2004; 364(9452):2188-95.
94 Del Rosso JQ, Webster GF, Jackson M, et al. Two randomized phase III clinical trials evaluating anti-inflammatory dose doxycycline (40-mg doxycycline, USP capsules) administered once daily for treatment of rosacea. J Am Acad Dermatol. 2007; 56(5):791-802.
95 Fleischer AB Jr, Dinehart S, Stough D, et al. Safety and efficacy of a new extended-release formulation of minocycline. Cutis. 2006; 78(4 Suppl):21-31.
96 Del Rosso JQ, Preston NJ, Caveny SW, and Gottschalk RW. Effectiveness and safety of modified-release doxycycline capsules once daily for papulopustular rosacea monotherapy results from a large community-based trial in subgroups based on gender. J Drugs Dermatol. 201211; (6):703-7.
97 Garner SE, Eady EA, Popescu C, et al. Minocycline for acne vulgaris: efficacy and safety. Cochrane Database Syst Rev. 2012 Aug 15; 8:CD002086.